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Low-dose thalidomide in myelofibrosis

Allogeneic stem cell transplant is the only potentially curative treatment for myelofibrosis, but is often precluded by advanced age, poor performance status or copathologies.[1] Increased marrow angiogenesis occurs in myelofibrosis and greater neovascularization correlates with poorer prognosis,[2] stimulating interest in thalidomide therapy. Doses of 100-400mg daily reduced transfusion requirement and splenomegaly in some patients, but were poorly-tolerated.[3] Low-dose thalidomide starting at 50mg daily with/without a tapering dose of prednisolone is reported to be well-tolerated and effective.[4,5]

We investigated 15 patients treated with low-dose thalidomide (50 mg daily) for myelofibrosis in our centers. The study was approved by the ethics committee at St Thomas' Hospital. All patients met consensus criteria for myelofibrosis.[6] Clinical parameters are summarized in Table 1. Median follow-up was eight months.

All patients initially received oral thalidomide 50 mg daily. Thirteen patients also received oral prednisolone at 30-60 mg (0.5-1mg/kg) daily; tapered over 12 weeks. Responses were confirmed according to European Myelofibrosis Network (EUMNET) criteria;[7] the International Working Group consensus criteria[8] were not used since no patient had repeated bone marrows.

Before treatment, 7 patients (47%) were transfusion dependent (mean requirement 5.9 units over six months, range 0–21); 6 had platelet counts < 100×10^9/L (mean 157×10^9/L, range 32–487×10^9/L). All non-splenectomized patients had palpable splenomegaly (mean 10 cm; range 1–26 cm).

After low dose thalidomide ±prednisolone the overall transfusion requirements were unchanged (mean 6.0 units/six months), 3 out of 7 (43%) transfusion-dependent patients had a fall in transfusion requirement after thalidomide, 2 became transfusion independent. However, 3 patients progressed and required transfusion. There was no significant rise in mean platelet counts (157×10^9/L pre-treatment, 184×10^9/L post-treatment). Splenomegaly was reduced by more than 50% in 4 out of 13 (31%) patients. Median white cell count remained unchanged.

Overall responses according to EUMNET criteria were: no complete responses, five major responses (33%), one moderate response (7%), and five minor responses (33%). Four patients (27%) had no response. Median time to peak response was 7.5 weeks (range 2–15 weeks). Seven patients both had a response and did not stop thalidomide early because of adverse effects; the median response duration was 16 weeks (4–95 weeks). For 3 patients, response was lost when prednisolone stopped at week 12. The 2 patients not treated with prednisolone demonstrated a minor and no response respectively. Five out of 13 patients (38%) were positive for the *JAK2V617F* mutation and were indistinguishable from negative patients.[9]

Four patients (27%) developed grade 1/2 peripheral neuropathy; 2 grade 1/2 constipation while somnolence was reported in one patient. No proven thromboembolism occurred, but one patient with pneumonia and marked leukocytosis died following an unconfirmed pulmonary embolism. There was no neutropenia or increased myeloproliferation. One patient experienced weight gain and folliculitis ascribed to steroids. Eleven patients had stopped thalidomide by the end of the study due to: lack/loss of hematologic response

Table 1. Patients' characteristics and responses.

Patient n.	*Primary or secondary*	*JAK-2 mutation*	*Prednisolone*	*Lille score*	*Age (yrs)*	*Sex*	*Prior treatments*	*EUMNET response*
1	Secondary to ET	Negative	Yes	1	60	F	Danazol, IFNα, HU	No response
2	Primary	Negative	Yes	1	80	M	None	Major
3	Secondary to ET	Positive	Yes	0	70	M	HU, IFNa, HU	Minor
4	Secondary to ET	–	Yes	2	83	M	Busulfan, danazol	No response
5	Secondary to PV	Positive	No	1	78	F	HU, busulfan	No response
6	Primary	Negative	Yes	1	70	M	Danazol, EPO, steroids	Minor
7	Primary	Negative	Yes	1	78	F	Anagrelide	Minor
8	Primary	Negative	Yes	1	65	M	None	Major
9	Primary	Negative	Yes	1	73	M	HU, splenectomy	No response
10	Primary	Positive	Yes	2	54	M	None	Major
11	Secondary to ET	Negative	No	0	58	M	HU	Minor
12	Secondary to PV	–	Yes	1	52	F	HU, splenectomy, steroids	Minor
13	Primary	Negative	Yes	1	50	M	None	Moderate
14	Primary	Positive	Yes	2	53	M	None	Major
15	Primary	Positive	Yes	1	64	M	HU	Major

ET: essential thrombocytosis; PV: polycythemia vera; F: female; M: male; HU: hydroxycarbamide (hydroxyurea); IFNα: interferon α; EPO: erythropoietin. Lille score: Dupriez et al., 1996. EUMNET response criteria: Barosi et al., 2005.

(n=6), neuropathy (n=3), development of an unrelated malignancy (glioblastoma) (n=1), reduced-intensity allogeneic transplantation (n=1).

This is the first study to use internationally agreed response criteria for myelofibrosis (the EUMNET criteria) to evaluate response to thalidomide and prednisolone. Overall, 40% of patients achieved major or moderate responses by EUMNET criteria. All responses began within the first 12 weeks of treatment, suggesting that thalidomide could be stopped if there is no response by this time. Among responders, the median response duration was 16 weeks. Three patients lost their responses when prednisolone was withdrawn at 12 weeks. The 2 patients not treated with prednisolone appeared to have a less favourable response.

Our results are consistent with those of phase II trials.[4] In the Mesa trial,[4] 40% became transfusion independent, 75% had a >50% rise in platelet count, and 19% had a >50% reduction in spleen size. In the Marchetti trial,[5] 39% became transfusion independent, 22% had a >50x10^9/L rise in platelet count, and 19% had a >50% reduction in spleen size.

The relative importance of thalidomide and prednisolone when used in combination is unclear, but prednisolone seems to be partly responsible for responses. Case reports suggest that corticosteroids have efficacy as monotherapy in myelofibrosis.[9] However, our response rates are similar to those obtained with thalidomide monotherapy (median 100 mg/d). Three of our patients experienced a loss of clinical response when prednisolone was stopped consistent with other studies[4] and 2 patients not treated with prednisolone showed a poorer performance.

Our data confirms that low-dose thalidomide with prednisolone is effective treatment for myelofibrosis, leading to transfusion independence, improvement in thrombocytopenia and reduction in spleen size in some patients. We recommend assessment of thrombotic risk and thromboprophylaxis for high-risk patients. Low-dose thalidomide is not effective in all patients, and responses are often not sustained after withdrawal of prednisolone.

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Increased cortical bone mineralization in imatinib treated patients with chronic myelogenous leukemia

Imatinib mesylate (Glivec®, Gleevec™, Novartis International AG) and the second generation ABL tyrosine kinase inhibitors have markedly improved the outcome of patients with chronic myeloid leukemia (CML). More patients are receiving treatment with these inhibitors for prolonged periods of time and experience with imatinib now exceeds five years. The immediate side effects are usually mild and manageable. There have been recent reports on the long-term side effects associated with prolonged use of imatinib.[1-3] Berman and coworkers found that imatinib treated patients had hypophosphatemia, lower osteocalcin levels and higher parathyroid hormone levels.[2] Subsequent studies confirmed the observation of hypophosphatemia in patients receiving imatinib.[4-8] The authors concluded that imatinib may affect bone remodeling and if left untreated, chronic hypophosphatemia may result in impaired bone mineralization, rickets, and osteomalacia.[2]

We, therefore, investigated bone mineral density (BMD) in imatinib treated CML patients and healthy controls. All imatinib treated CML patients at Sahlgrenska University Hospital were identified of whom 17 fulfilled the study inclusion criteria: (i) imatinib treatment duration ≥24 months, and (ii) first chronic phase of the disease with complete cytogenetic remission. The inclusion criteria were set to minimize the confounding effect of leukemia and to allow time for a pos-